(b) testing the 1000 or more samples for solubility of the active pharmaceutical ingredient in each sample; and

(c) comparing the solubilities of each sample to a baseline or a control for the solubility to generate a comparison result for each sample.

Please add the following new claim:

129. (New) The method of claim 30, wherein at least one sample has decreased solubility and at least one sample has a synergistic increased solubility.

Remarks

Applicants first wish to thank Examiner Baker for the courtesy she extended to Attorneys for Applicants, Anthony M. Insogna and Max Bachrach, during the interview held on January 7, 2003.

Claims 31, 32 and 36 are canceled without prejudice to Applicants' rights to pursue them in one or more continuation, divisional or continuation-in-part applications. Claim 30 is amended as shown in Appendix A, attached hereto, to recite various limitations that are properly supported by the specification. For example: the support for "testing solubility" can be found on page 10, lines 9-18 of the specification; the support for "active pharmaceutical ingredient" can be found on page 9, lines 4-9 of the specification; the support for "1000 or more samples" can be found on page 7, lines 21-22 of the specification; the support for "100 mg or less" can be found on page 7, lines 31-32 of the specification; and the support for "at least three excipients" can be found on page 7, lines 25-26 of the specification.

New claim 129 is added to recite another aspect of the present invention. The support for this new claim can be found, for example, on page 16, line 25 - page 17, line 8 of the specification. No new matter has been introduced.

The Rejection Under 35 U.S.C. § 102(b) in View of U.S. Patent No. 5,503,843 Should Be Withdrawn

On page 3 of the Office Action, claims 30-34 and 126 are rejected as allegedly anticipated by U.S. Patent No. 5,503,843 to Santus et al. ("Santus"). In particular, it is alleged that Santus discloses a method of high-throughput transdermal formulations for the skin permeation, which reads on the claims 30-34 and 126 of the present application.

Although Applicants respectfully disagree with the substance of this rejection, claim 30 is amended to recite that the samples comprise at least three excipients and that 1000 or more samples are tested. In light of this amendment, Santus fails to teach every element of the amended claim 30, thus Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) should be withdrawn.

The Rejection Under 35 U.S.C. § 102(b) in View of U.S. Patent No. 5,490,415 Should Be Withdrawn

On page 4 of the Office Action, claims 30-34, 40, 126 and 127 are rejected in view of U.S. Patent No. 5,490,415 to Mak et al. ("Mak"). It is alleged that because Mak discloses an apparatus for testing diffusion and solubility of a drug, the cited claims are anticipated by the disclosure of Mak.

Again, in light of the amendment made to claim 30 of the present application, Mak fails to disclose every element of the cited claims as amended. Therefore, Applicants respectfully submit that the rejection under 35 U.S.C. § 102(b) in view of Mak should be withdrawn.

The Rejection Under 35 U.S.C. § 102(b) in View of Takai et al. Should Be Withdrawn

On page 5 of the Office Action, claims 30-33, 35, 126 and 128 are rejected in view of Takai et al., *Chem. Pharm. Bull.* (1984) ("Takai"). In particular, it is alleged that because Takai disclosed a computer optimization technique for determination of optimum formulations of griseofulvin, it reads on the cited claims.

However, Applicants respectfully point out that Takai is silent about high-throughput screening of an array of samples. Moreover, in light of the amendment to claim 30 to recite the amount of the active ingredient, Takai by no means reads on the cited claims of the present application. Therefore, Applicants respectfully request that this rejection should be withdrawn.

The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 6 of the Office Action, claims 30-43 and 126-128 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over any of Santus, Mak or Takai, in view of U.S. Patent No. 5,985,214 to Stylli et al. ("Stylli"). As admitted in the Office Action, neither Santus, Mak nor Takai discloses the specific numbers or amounts of compounds used in the

claimed methods. However, it is alleged that because Stylli discloses the optimization of such variables, which is well-established in the art, the present invention is obvious over the combination of the cited references. Applicants respectfully traverse this rejection for the following reasons.

As the Examiner is well aware, to establish *prima facie* case of obviousness, it is required that the alleged prior art teach or suggest all of the limitations of the claims alleged to be obvious. *In re Royka,* 490 F.2d 981 (CCPA 1974) (holding that to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art). Applicants respectfully submit that such a requirement is not met by the references cited by the Examiner.

Stylli does not teach or suggest the amounts or numbers of the compounds used in the method of this invention. All Stylli does is to disclose that pharmaceutical formulations and pharmaceutically effective amount of active ingredients can be determined by the methods well-known in the art. *See, e.g.*, Stylli, columns 43 and 44. However, amended claim 30 recites that the amount of the active ingredient of less than about 100 mg and that 1000 or more samples are being tested. Moreover, the amended claim 30 recites that at least three excipients are present in the samples. Applicants respectfully submit that the invention as recited by the amended claim 30 has nothing to do with the optimization techniques disclosed by Stylli. In other words, the amount of 100 mg, the sample number of 1000, or the presence of three or more excipients, as recited by claim 30, is not a figure obtained from the effort to optimize a pharmaceutical composition. Rather, the presently claimed invention is directed to testing the solubility of an active pharmaceutical ingredient and rapidly and efficiently determining the effect of multiple excipients on that property. Therefore, because none of the cited references disclose or suggest a high-throughput method of systematically determining the effect of three or more excipients on the solubility of an active pharmaceutical ingredient, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

For the foregoing reasons, Applicants respectfully submit that the pending claims are in an allowable form.

No fee is believed to be due for the submission of this response. Should any additional fees be required, however, please charge the required fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully Submitted,

Date: March 10, 2003

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APPENDIX A

Marked-Up Copy of the Amended Claims

Please cancel claims 31, 32 and 36 without prejudice.

Please amend claim 30 to provide the following:

30. (Twice Amended) A method for testing [or optimizing one or more properties of a formulation] solubility of an active[-component] pharmaceutical ingredient in a sample, comprising:

(a) preparing an array comprising 1000 or more [of] samples, each sample comprising less than about 100 mg of the active [component] pharmaceutical ingredient and at least [one additional component] three excipients, wherein each sample differs from any other sample with respect to at least one of:

(i) the identity of [the additional component] an excipient, or

(ii) the ratio of the active [component] pharmaceutical ingredient to [the additional component, or] an excipient;

[(iii) the physical state of the active component;]

(b) testing [each sample] the 1000 or more samples for [at least one property to generate a property-result for] solubility of the active pharmaceutical ingredient in each sample; and

(c) comparing the [property-result generated for] solubilities of each sample to a baseline or a control for [said property] the solubility to generate a comparison result for [the] each sample.